

EXHIBIT

A

Example 1

Dr. Goodman's analysis of Bove 2014 (Civ. Mort. Study) from her Parkinson's charts being incorporated directly into the body of her Parkinson's report.

Trichloroethylene, Perchloroethylene, Benzene, Vinyl Chloride, and *trans*-1,2-Dichloroethylene and Parkinson's Disease

Prepared by



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Table C.1 PD Epidemiology Study Quality Assessment

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Cohort Studies										
Bove et al. (2014a)	Civilian employees at CL and CP	I	P	B	V	<u>Strengths</u> <ul style="list-style-type: none">• Appropriate comparison groups• ≤ 2% loss to follow-up <u>Weaknesses</u> <ul style="list-style-type: none">• Most of the cohort was < 65 yrs old by end of follow-up (> 70% CL, > 60% CP)	<u>Strengths</u> <ul style="list-style-type: none">• No missing data• Internal analyses considered duration of employment and average exposure <u>Weaknesses</u> <ul style="list-style-type: none">• Indirect chemical exposure measurement – based on employment at CL (external analyses) or modeling of groundwater contamination (internal analyses)• External analyses did not consider duration of employment and average exposure	<u>Strengths</u> <ul style="list-style-type: none">• Deaths identified from SSA, a commercial tracing service, and NDI; cause of death determined from NDI Plus• No missing data <u>Weaknesses</u> <ul style="list-style-type: none">• Assessed mortality only	<u>Strengths</u> <ul style="list-style-type: none">• Controlled for: age, and sex in US comparison and sex and occupation in CP and internal comparisons• Considered but did not control for: age in CP and internal comparisons because adjusted vs. unadjusted results differed by < 10%• Collected occupation data quarterly during employment <u>Weaknesses</u> <ul style="list-style-type: none">• Did not consider or control for: genetic factors or family history of PD, alcohol intake, smoking in any analyses, or other potential occupational exposures in US comparison• Unclear whether occupation was analyzed in a time-varying manner, other covariates only considered at a single time point	<u>Strengths</u> <ul style="list-style-type: none">• Employment histories collected separately from outcome data• Appropriate consideration of latency <u>Weaknesses</u> <ul style="list-style-type: none">• No major weaknesses

Bove *et al.* (2014a) ascertained vital status through linkage of personal identifier information from the Defense Manpower Data Center (DMDC) database to data from the Social Security Administration (SSA) Death Master File, SSA Office of Research, Evaluation and Statistics (ORES) Presumed Living Search. Of the combined Camp Lejeune and Camp Pendleton cohorts, almost 50% of study participants were reportedly not able to be uniquely matched to the ORES file or their vital status was listed as "unknown." For those individuals, a commercial tracing service was used to obtain information on vital status. Identified deaths and individuals whose vital status remained unknown were then searched in the National Death Index (NDI). If vital status remained unknown after the NDI search, those participants were considered lost to follow-up. Underlying and contributing causes of death information were obtained from NDI Plus.

Between 1979 and 2008, Bove *et al.* (2014a) observed only five PD deaths in the Camp Lejeune cohort, which is reflected in the wide CIs of risk estimates. The authors computed a SMR and 95% CI comparing the Camp Lejeune and Camp Pendleton cohorts to the age, sex, race, and calendar period-specific US mortality rate. The authors found no statistically significant evidence of an increased PD mortality risk among Camp Lejeune civilian employees compared to what was expected based on rates in the US general population (SMR = 2.19, 95% CI: 0.71-5.11).

In comparisons of PD mortality between the Camp Lejeune and Camp Pendleton cohorts, Bove *et al.* (2014a) relied on Cox extended regression models with age as the time variable and base location as a time-varying dichotomous variable to calculate HRs. No statistically significant difference in mortality rates was observed when Camp Lejeune civilian employees were compared to civilian employees at Camp Pendleton (HR = 3.13, 95% CI: 0.76-12.86), after implementing a 10-year lag that was selected based on Akaike's information criterion (AIC).

Within the Camp Lejeune cohort, Bove *et al.* (2014a) evaluated exposure-response relationships based on cumulative exposures to drinking water contaminants using Cox extended regression models with age as the time variable and cumulative exposure as a time-varying variable. Cumulative exposures ($\mu\text{g/L-years}$) were based on monthly average contaminant concentrations in the Hadnot Point water system and dates of employment at Camp Lejeune. Because cumulative exposures to contaminants were correlated, each model included only one contaminant at a time. To identify potential confounding, the authors required that the covariate change the risk estimate by 10%. The final Cox models included sex, race, occupation (blue collar vs. white collar), and education level.

Bove *et al.* (2014a) did not observe a statistically significant increase in risk among employees with maximum cumulative exposures \geq median for TCE (HR = 2.51, 95% CI: 0.21-30.76), PCE (HR = 2.68, 95% CI: 0.22-33.28), benzene (HR = 2.52, 95% CI: 0.20-31.59), or vinyl chloride (HR = 2.81, 95% CI: 0.23-34.11) when compared to those with maximum cumulative exposures $<$ median after implementing a 10-year lag. In addition, the authors evaluated exposure-response relationships using both continuous and \log_{10} continuous cumulative exposure models. The log transformed data provided a better model fit and better captured the exposure-response relationship. There was no increased risk of PD mortality associated with any chemical in the log-transformed models.

5.1.2 Quality Considerations

Study Population. This study had no obvious risk of selection bias, had low loss to follow-up ($< 2\%$), and used appropriate comparison groups. Most of the cohort was younger than 65 years of age at the end of the study, less than 15% of the study population had died, and only a small number of PD deaths were observed ($n = 5$), which resulted in wide CIs and limited the precision of the estimated associations.

Exposure Assessment. In external comparisons to the US and Camp Pendleton populations, there was no consideration of chemical-specific exposures or doses. Potential exposures used for comparisons within the Camp Lejeune cohort were estimated based on groundwater fate and transport models of the monthly average concentrations of chemicals in the water distribution system that supplied most of the civilian workplace locations. Workers were considered exposed to the modeled monthly average water concentration for every month they were employed. These direct measurements are more reliable than exposure estimates that are not based on any quantitative information, but without a direct link to information on individual-level water consumption/exposures, they are likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures based on chemical concentrations in the groundwater supplying different locations on base depends on the accuracy of the model's assumptions, and while the time-varying nature of the exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-term or even average exposure concentrations. Therefore, exposure misclassification is likely. In a recent deposition, Bove (2024a) acknowledged the uncertainty regarding the assessment of time spent at the main area served by Hadnot Point, the lack of information on water consumption, and that the assumption that all workers lived off base was incorrect.

Outcome Assessment. The study assessed PD mortality, which is a serious limitation because PD is not a fatal disease. Reliable sources were used to identify deaths (*i.e.*, SSA, commercial tracing service, NDI).

Covariates Considered. The authors controlled for age and sex in the US comparison, and age, sex, and occupation (blue vs. white collar) as a proxy for other chemical exposures in the Camp Pendleton and internal comparisons. The authors did not consider or control for other potential occupational exposures in the external comparison to the US population, genetic factors, a family history of PD, alcohol intake, or smoking in any analyses, which could have resulted in uncontrolled confounding. Bove (2024a) stated, "Because cumulative exposures to the contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease, each Cox regression model included only one contaminant at a time or TVOC." Therefore, it is unlikely that co-exposures were fully controlled in the model, and residual confounding is likely. In addition, while the authors collected occupational data quarterly, it is unclear if they analyzed those data in a time-varying manner, and the amount of missing covariate data was not reported, which limits the ability to fully interpret the results.

Temporality. Employment histories were collected separately from outcome data and an appropriate latency period was considered (*e.g.*, 10-year lag).

5.1.3 Conclusion

Bove *et al.* (2014a) did not observe statistically significant associations between being a civilian employee at Camp Lejeune and PD mortality in comparisons with the US mortality rate and the Camp Pendleton cohort. In chemical-specific analyses based on maximum cumulative exposures within the Camp Lejeune cohort, no changes in risk were reported for dichotomous (\geq median vs. $<$ median) or continuous log-transformed exposures. These analyses were all based on only five individuals who died of PD at Camp Lejeune, making results difficult to interpret. Most importantly, although the study was able to rely on direct chemical exposure assessments, the authors were not able to account for important exposure information (*e.g.*, ingestion rates) to accurately assess individual exposure, and all chemical exposures were highly correlated with each other, limiting any chemical-specific conclusions. The study also failed to incorporate all relevant covariates, which may have resulted in some confounding bias. Overall, this study does not provide evidence for an association between TCE, PCE, benzene, or vinyl chloride and PD mortality.

Example 2

Dr. Goodman's analysis of Carreon (2014) from her kidney cancer charts being incorporated directly into the body of her kidney cancer report.

Trichloroethylene, Perchloroethylene, Benzene, Vinyl Chloride, and *trans*-1,2-Dichloroethylene Exposure and Kidney Cancer

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Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							individuals (e.g., no water consumption information)		diabetes, or alcohol consumption <ul style="list-style-type: none"> Did not include relevant covariates in a time-varying manner (i.e., occupation) Amount of missing data is unknown 	
Carreón <i>et al.</i> (2014)	Workers at a chemical manufacturing plant				V	<u>Strengths</u> <ul style="list-style-type: none"> Appropriate study and comparison groups 2% loss to follow-up <1% excluded <u>Weaknesses</u> <ul style="list-style-type: none"> No major weaknesses 	<u>Strengths</u> <ul style="list-style-type: none"> Semiquantitative exposure estimate (i.e., considered duration) No missing data <u>Weaknesses</u> <ul style="list-style-type: none"> Indirect chemical exposure measurement (i.e., employment at facility) Did not assess time-varying nature of exposure 	<u>Strengths</u> <ul style="list-style-type: none"> Deaths identified using reliable sources (i.e., NDI, NDI Plus, and Florida Department of Health) 48 yrs of follow-up <u>Weaknesses</u> <ul style="list-style-type: none"> Assessed mortality only 	<u>Strengths</u> <ul style="list-style-type: none"> Controlled for: age, sex, and race/ethnicity <u>Weaknesses</u> <ul style="list-style-type: none"> Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures 54.2% missing race/ethnicity; assumed white 	<u>Strengths</u> <ul style="list-style-type: none"> Exposure documented before outcome <u>Weaknesses</u> <ul style="list-style-type: none"> No consideration of latency

9 Vinyl Chloride and Kidney Cancer

In this section, I describe epidemiology and toxicity studies that assessed vinyl chloride exposure and kidney cancer, and government and other agency reviews of this evidence. I conclude that scientific evidence does not support a causal association between vinyl chloride and kidney cancer.

9.1 Epidemiology

9.1.1 Overview

I identified eight cohort studies that evaluated vinyl chloride exposure and kidney cancer; I did not identify any case-control studies. All these studies were conducted in the US and, collectively, they evaluated four unique populations. I review here all studies in populations at Camp Lejeune where vinyl chloride exposures were specified, even if overlapping, for completeness. I provide an overview, including a brief discussion of study characteristics and quality, below, and this is reviewed in more detail in Attachment C, Table C.1, and Attachment J, Table J.1. Study results are discussed briefly in Section 9.1.2 and reviewed in more detail in Attachment J, Table J.2. Epidemiology evidence is integrated with experimental evidence in Section 9.3.

9.1.1.1 Study Population

Vinyl chloride exposure and kidney cancer risk was evaluated in three studies of populations living or working at Camp Lejeune (Bove *et al.*, 2014a,b; ATSDR, 2018b), one study of vinyl chloride or PVC resin manufacturing workers (Mundt *et al.*, 2017), one study of workers at a chemical manufacturing plant (Carreón *et al.*, 2014), and one study of employees of the Union Carbide Corporation's Chemicals and Plastics business group (Teta *et al.*, 1990). Exposed and unexposed participants were selected from the same source population in all studies. Bove *et al.* (2014a,b) did not report whether any participants were excluded from their analyses and ATSDR (2018b) reported low participation rates. ATSDR (2018b) actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known, which increased the potential for selection bias. As discussed in Section 5, ATSDR (2018b) noted that in its Camp Lejeune study, selection bias could have biased results away from the null. Three of the studies reported <25% loss to follow-up (Carreón *et al.*, 2014; Teta *et al.*, 1990; Mundt *et al.*, 2017).

9.1.1.2 Exposure Assessment

I assume that most participants in the Mundt *et al.* (2017), Carreón *et al.* (2014), and Teta *et al.* (1990) studies were exposed to vinyl chloride *via* inhalation or dermally, while exposures in the Camp Lejeune studies could have been *via* ingestion, inhalation, or dermal absorption.

The most critical limitation in all of the studies was the manner by which exposures were estimated. Three of the studies (Carreón *et al.*, 2014; Teta *et al.*, 1990; Mundt *et al.*, 2017) assigned exposure based on whether someone was employed at a PVC factory for at least 1 year. Bove *et al.* (2014a,b) and ATSDR (2018b) estimated individual exposures at Camp Lejeune using modeled average monthly levels of

9.1.1.5 Temporality

All of the studies had documented exposures prior to the onset of disease. Bove *et al.* (2014a,b) appropriately incorporated 10-year lags into some of their analyses. ATSDR (2018b) and the other three studies did not consider disease latency in their analyses (Carreón *et al.*, 2014; Teta *et al.*, 1990; Mundt *et al.*, 2017). The possible inclusion of cases in analyses that could have occurred within 4 years of participants' first exposures undermined their ability to properly assess an exposure-outcome relationship.

9.1.2 Study Results

The cohort studies reported risk estimates ranging from 0.39-1.84 for the relationship between vinyl chloride exposure and kidney cancer. The only exception is Bove *et al.* (2014b), which reported a risk estimate of infinity when comparing Camp Lejeune civilian employees with \geq median maximum cumulative vinyl chloride exposure to those with $<$ median maximum exposures because all kidney cancer deaths in civilian employees occurred in the higher exposure group.

The only statistically significant risk estimate was reported in ATSDR (2018b), in a comparison of Camp Lejeune Marines and Navy personnel with medium cumulative exposure to those with low cumulative exposure (OR = 1.45, 95% CI: 1.05-2.00). However, the risk estimate comparing those with high cumulative exposure to those with low cumulative exposure was not significant (OR = 1.55, 95% CI: 0.95-2.54) (ATSDR, 2018b). The exposure metric in these analyses was not specific to vinyl chloride because TCE, benzene, vinyl chloride, and TVOCs were correlated (gamma coefficient >0.99) so analyses were only conducted for TCE (ATSDR, 2018b). Bove *et al.* (2014a) did not report an association between vinyl chloride exposure and kidney cancer for Marines and Navy personnel at Camp Lejeune with high cumulative exposure compared to those with low cumulative exposure (HR = 1.51, 95% CI: 0.61-3.74) or when comparing Marines and Navy personnel at Camp Lejeune with medium/high cumulative to Marines and Navy personnel at Camp Pendleton (HR: 1.55, 95% CI: 0.94-2.57).

There was no association between working in vinyl chloride or PVC resin manufacturing (SMR = 1.16, 95% CI: 0.87-1.53) (Mundt *et al.*, 2017), or working in a PVC, vinyl department, at a rubber and plastic chemical manufacturing plant (SMR = 0.64, 95% CI: 0.08-2.33) (Carreón *et al.*, 2014) and kidney cancer risk. Teta *et al.* (1990) reported no association in hourly male employees in a Chemicals and Plastics business group (SMR = 1.74, 95% CI: 0.75-3.43).

One study discussed by Plaintiffs' experts evaluated vinyl chloride exposure and kidney cancer risk and was published before the start date of my literature search (Attachment A) but was not included in the agency reports I reviewed. Hu *et al.* (2002) evaluated incident kidney cancer cases diagnoses between 1994 and 1997 in Canada. They evaluated exposure to vinyl chloride using questionnaires on job history. They reported an increased risk of kidney cancer in men with any exposure to vinyl chloride (OR = 2.0, 95% CI: 1.2-3.3). They also reported an increased risk of kidney cancer associated with vinyl chloride exposures for at least 20 years (OR = 4.5, 95% CI: 1.9-10.6) but not for shorter durations. Like most of the epidemiology studies I reviewed, this study had major methodological limitations, including the potential for exposure misclassification and residual and uncontrolled confounding.

9.1.3 Conclusions

Vinyl chloride and kidney cancer associations were evaluated in six studies of four populations, three of which were at Camp Lejeune. Most analyses do not provide evidence of associations or exposure-response relationships. All of these studies had critical methodological limitations, including that only three assessed

Example 3

Dr. Goodman's analysis of Gerin (1998) from her bladder cancer charts being incorporated directly into the body of her bladder cancer report.

Trichloroethylene, Perchloroethylene, Benzene, Vinyl Chloride, and *trans*-1,2-Dichloroethylene Exposure and Bladder Cancer Risk

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Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Teschke <i>et al.</i> (1997)	British Columbia general population		P			<u>Strengths</u> <ul style="list-style-type: none"> Appropriate case and control selection 88.2% and 80.3% enrollment rate in cases and controls, respectively <u>Weaknesses</u> <ul style="list-style-type: none"> No major weaknesses 	<u>Strengths</u> <ul style="list-style-type: none"> No missing data <u>Weaknesses</u> <ul style="list-style-type: none"> Indirect exposure measurement (<i>i.e.</i>, self-reported occupational history and proxies for cases and controls unable to respond) Qualitative exposure estimate (<i>i.e.</i>, based on occupational group) Potential for recall bias (<i>i.e.</i>, self-reported occupational history after diagnosis) 	<u>Strengths</u> <ul style="list-style-type: none"> Cases identified using a reliable source (<i>i.e.</i>, British Columbia Cancer Agency) and histologically confirmed Assessed disease incidence <u>Weaknesses</u> <ul style="list-style-type: none"> No major weaknesses 	<u>Strengths</u> <ul style="list-style-type: none"> Controlled for or considered: age, sex, smoking, history of bladder infections, prior cancer, or other occupational and non-occupational exposures <u>Weaknesses</u> <ul style="list-style-type: none"> Did not consider or control for: race/ethnicity or genetics Amount of missing data unknown 	<u>Strengths</u> <ul style="list-style-type: none"> Appropriate consideration of latency (5-, 10- and 15-yr lags) <u>Weaknesses</u> <ul style="list-style-type: none"> Unclear if exposure period included time after diagnosis
Gérin <i>et al.</i> (1998)	Canadian white males			B		<u>Strengths</u> <ul style="list-style-type: none"> Appropriate case selection 82% participation rate in cases <u>Weaknesses</u> <ul style="list-style-type: none"> Inappropriate control selection (<i>i.e.</i>, non-compulsory electoral lists) 71% participation rate in controls Case and control participation rates differed 	<u>Strengths</u> <ul style="list-style-type: none"> Semiquantitative exposure estimate (<i>i.e.</i>, considered duration, frequency, and intensity) No missing data <u>Weaknesses</u> <ul style="list-style-type: none"> Indirect chemical exposure measurement (<i>i.e.</i>, self-reported occupational history and expert opinion) Potential for recall bias (<i>i.e.</i>, self-reported occupational history after diagnosis) 	<u>Strengths</u> <ul style="list-style-type: none"> Cases identified using a reliable source (<i>i.e.</i>, medical records); vital status for controls confirmed <i>via</i> interview Assessed disease incidence <u>Weaknesses</u> <ul style="list-style-type: none"> No major weaknesses 	<u>Strengths</u> <ul style="list-style-type: none"> Controlled for or considered: age, sex, ethnicity, smoking, and co-exposures (toluene, xylene, styrene, and aromatic amines) <u>Weaknesses</u> <ul style="list-style-type: none"> Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics Amount of missing data unknown 	<u>Strengths</u> <ul style="list-style-type: none"> Exposure considered prior to diagnosis <u>Weaknesses</u> <ul style="list-style-type: none"> No consideration of latency

8 Benzene and Bladder Cancer

In this section, I describe epidemiology and toxicity studies that assessed benzene exposure and bladder cancer, and governmental and other agency reviews of this evidence. I conclude that the scientific evidence does not support a causal association between benzene and bladder cancer.

8.1 Epidemiology

8.1.1 Overview

I identified 44 cohort studies (in 26 unique populations), five case-control studies, one case-cohort study (Shala *et al.*, 2023; which I include in the case-control study tables) one pooled analysis of case-control studies and one meta-analysis that evaluated benzene exposure and bladder cancer. Most of these studies were conducted in North America or Europe, but there were also studies in Australia, South Korea, and China. I review here all studies in populations at Camp Lejeune where benzene exposures were specified, even if overlapping, for completeness. Otherwise, if several studies analyzed the same cohorts or population groups, I summarize only the most recent study because it had longer follow-up times and/or used more reliable exposure estimates, unless older studies reported additional results (*e.g.*, dose-response relationships). I provide an overview, including a brief discussion of cohort and case-control study characteristics, below and in Tables H.1 and H.3. Detailed study quality assessments are described in Table C.1. Study results are discussed in Section 8.1.2 and in Tables H.2, H.4, and H.5. Epidemiology evidence is integrated with experimental evidence in Section 8.3.

8.1.1.1 Study Population

In most cohort studies, exposed and unexposed participants were selected from the same source population. Individuals with and without bladder cancer were also drawn from appropriate populations in most case-control studies. There were two exceptions, Gérin *et al.* (1998) used electoral lists to identify potential controls in a population where voter registration was non-compulsory, and Hadkhale *et al.* (2017) allowed for cases and controls to have a prior history of cancer. Most cohort studies reported high retention rates, but did not always report rates of exclusion, and some of the case-control studies reported low (<80%) participation rates among controls; the latter two aspects increased the potential for selection bias. In all cohort and case-control studies that reported high loss to follow-up or low participation rates, the authors did not report information on how those who were included differed from those who were not, making the assessment of selection bias difficult. As discussed in Section 5, ATSDR (2018a) noted that in its Camp Lejeune study, selection bias could have biased results away from the null.

8.1.1.2 Exposure Assessment

I assume that most participants in occupational studies were exposed to benzene *via* inhalation or dermally, while participants in the Camp Lejeune studies could have been exposed *via* ingestion, inhalation, or dermal absorption.

The most critical limitation in all studies is the manner by which exposures were estimated. The cohort studies examining benzene exposure and bladder cancer were largely conducted among populations that represented specific occupational groups (e.g., transformer manufacturing workers in Greenland *et al.* [1994]; petroleum or oil refinery workers in Tsai *et al.* [2007]). All studies estimated benzene exposure in an indirect manner, based on job title/history or whether individuals were ever/never exposed to benzene at work, job histories linked to a JEM, or the presence of benzene in drinking water (Camp Lejeune studies). There were no directly measured air or water exposure concentrations evaluated at the individual level in any studies.

Bove *et al.* (2014b) and ATSDR (2018a) estimated individual exposures at Camp Lejeune using modeled average monthly levels of chemicals in drinking water on base, based on groundwater fate and transport models calculated in ATSDR (2007b, 2013), along with information on historical occupation codes, workplace or residence, and period and duration of employment or residence. As discussed in Section 5.1.2, these estimates are unreliable and biased high (ATSDR, 2017b; Hennet, 2024; Spiliotopoulos, 2024). However, neither study had individual water consumption/exposure data, so individual exposures were likely misclassified to some degree. In addition, there was a high correlation between some of the chemical-specific categorical exposure variables in Bove *et al.* (2014b) and ATSDR (2018a), which limits the interpretation of the benzene-specific results.

All case-control studies characterized exposure based on job histories or job histories linked to JEMs. In a few of the studies, job history information was recorded prior to the outcome (e.g., Greenland *et al.*, 1994; Shala *et al.*, 2023), but in three studies, self-reported job histories were collected after bladder cancer had been diagnosed (Steineck *et al.*, 1990; G  rin *et al.*, 1998; Pesch *et al.*, 2000). Self-reported exposure information is subject to potential recall inaccuracy due to the long time period between chemical use or exposure and interviews, and potential recall bias where cases may have recalled exposures differently than controls.

Most studies did not consider the frequency, duration, or intensity of potential exposures. The studies that accounted for exposure dose did so based on a JEM, duration of employment, or modeled drinking water contamination (with no individual consumption data); these indirect measurements are often crude and generally do not reflect actual individual exposure levels. In addition, most of the studies did not consider the time-varying nature of potential exposures (e.g., exposure was measured or estimated at a single time point or incorporated into the statistical model as a single value).

8.1.1.3 Outcome Assessment

Bladder cancer outcomes were obtained or confirmed using reliable and complete methods in most cohort and case-control studies, and all studies had sufficient follow-up time (*i.e.*, ≥ 5 years). For example, the cohort and case-control studies identified or confirmed cases using medical records, registries, or government databases (e.g., a national death index) except for Greenland *et al.* (1994), where only a subset of the cases identified from employee pension records were medically confirmed. A few studies may have had incomplete ascertainment of cases, namely when relying on self-report to identify cases without another source of identification (such as a registry to identify cases who did not self-report or who were deceased, e.g., ATSDR [2018a]). Most studies reported on bladder cancer incidence or mortality specifically. Eight studies (Satin *et al.*, 1996; Lewis *et al.*, 2000a; Wong *et al.*, 2001a,b; Tsai *et al.*, 2003; Huebner *et al.*, 2004; Tsai *et al.*, 2007; Collins *et al.*, 2015) reported cancers of the bladder and other urinary organs combined, and two studies (Steineck *et al.*, 1990; Pesch *et al.*, 2000) reported on urothelial cancers, which did not provide an accurate estimate of the benzene/bladder cancer-specific association.

Example 4

**Dr. Goodman's analysis Bloemen (2004) in her NHL charts being
incorporated directly into the body of her NHL report.**

Trichloroethylene, Perchloroethylene, Benzene, Vinyl Chloride, and *trans*-1,2-DCE Exposure and NHL Risk

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Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bloemen <i>et al.</i> (2004)	US chemical workers exposed to benzene			B		<u>Strengths</u> <ul style="list-style-type: none"> Appropriate study and comparison groups <u>Weaknesses</u> <ul style="list-style-type: none"> Unknown loss to follow-up Unknown number of exclusions 	<u>Strengths</u> <ul style="list-style-type: none"> No missing data <u>Weaknesses</u> <ul style="list-style-type: none"> Indirect exposure measurement in individuals (<i>i.e.</i>, employment in benzene exposed job ≥ 1 mo based on work history and IH expert opinion) Qualitative exposure estimate (<i>i.e.</i>, ever employed) Did not assess time-varying nature of exposure 	<u>Strengths</u> <ul style="list-style-type: none"> Deaths identified using reliable sources (<i>i.e.</i>, company research database via HR records, NDI, state vital statistics bureaus, and other sources) 57 yrs of follow-up <u>Weaknesses</u> <ul style="list-style-type: none"> Assessed mortality only 	<u>Strengths</u> <ul style="list-style-type: none"> Controlled for: age, sex, and race No missing data <u>Weaknesses</u> <ul style="list-style-type: none"> Did not control for or consider: family history of NHL or other potential chemical/occupational exposures 	<u>Strengths</u> <ul style="list-style-type: none"> No major strengths <u>Weaknesses</u> <ul style="list-style-type: none"> No consideration of latency Unclear if exposure measured before outcome
Huebner <i>et al.</i> (2004)	Employees at two US oil refineries and petrochemical facilities			B		<u>Strengths</u> <ul style="list-style-type: none"> Appropriate study and comparison groups $\leq 2\%$ loss to follow-up <u>Weaknesses</u> <ul style="list-style-type: none"> Unknown number of exclusions 	<u>Strengths</u> <ul style="list-style-type: none"> Semiquantitative exposure estimate (<i>i.e.</i>, considered duration) $\leq 1\%$ missing data <u>Weaknesses</u> <ul style="list-style-type: none"> Indirect chemical exposure measurement (<i>i.e.</i>, company records and work histories) Did not assess time-varying nature of exposure 	<u>Strengths</u> <ul style="list-style-type: none"> Deaths identified using reliable sources (<i>i.e.</i>, benefits records, NDI, and SSA) 28 yrs of follow-up <u>Weaknesses</u> <ul style="list-style-type: none"> Assessed mortality only 	<u>Strengths</u> <ul style="list-style-type: none"> Controlled for or considered: age, sex, and race/ethnicity No missing data <u>Weaknesses</u> <ul style="list-style-type: none"> Did not control for or consider: family history of NHL or other potential chemical/occupational exposures 	<u>Strengths</u> <ul style="list-style-type: none"> Exposure documented before outcome <u>Weaknesses</u> <ul style="list-style-type: none"> No consideration of latency

Most case-control studies characterized exposure based on self-reported or workplace information collected after NHL had been diagnosed. Self-reported exposure information is subject to potential recall inaccuracy due to the long period between chemical use or exposure and interviews, and potential recall bias can occur when cases recall exposures differently than controls.

Approximately two-thirds of the studies considered frequency, duration, or intensity of potential exposures. The studies that attempted to account for exposure levels often did so based on modeled contamination in drinking water (with no individual consumption data), JEMs, expert opinion, or duration of/time since first employment; these indirect measurements are at best crude estimates of actual exposures with an unknown amount of error. Most cohort studies did not consider the time-varying nature of potential exposures (*e.g.*, exposure was measured or estimated at a single time point or incorporated into the statistical model as a single value).

8.1.1.3 Outcome Assessment

As discussed in Section 4.2, the classification and definition of NHL has evolved overtime, including the inclusion or exclusion of different subtypes (*e.g.*, CLL). As a result, there are varying degrees of misclassification of NHL cases in epidemiology studies.

In epidemiology studies of benzene and NHL, NHL diagnoses were obtained or confirmed using reliable and complete methods for most cohort and case-control studies. Four studies were unable to confirm or validate reported NHL outcomes for all study subjects (*e.g.*, Blair *et al.*, 1989; Greenland *et al.*, 1994; Sorahan *et al.*, 2005; Saberi Hosnijeh *et al.*, 2013) and two studies did not report how NHL outcomes were identified (Fu *et al.*, 1996; Wang *et al.*, 2009). NHL cases and deaths were typically identified using medical records, registries, or government or national databases (*e.g.*, NDI, SSA) in both cohort and case-control studies. Most studies reported on NHL incidence or mortality, while a few reported on CLL and other subtypes (*e.g.*, mantle cell lymphoma, follicular lymphoma, Burkitt lymphoma), and some reported on lymphosarcoma and reticulosarcoma combined. Most cohort studies assessed NHL mortality only, which I consider weaker than those studies that evaluated NHL incidence.

8.1.1.4 Covariates Considered

Almost all epidemiology studies have some residual or uncontrolled confounding, which can bias results in either direction. All cohort and case-control studies reviewed here controlled for age and sex, except for Collins *et al.* (2003), which did not report if they considered sex, and Bernard *et al.* (1984), which did not control for age. Race/ethnicity were controlled for less consistently, and family history of NHL and other potential chemical or occupational exposures were rarely controlled for. Even when data on other potential chemical or occupational exposures were collected, none accounted for their time-varying nature. Approximately one-third of the cohort and case-control studies also did not provide information on the degree or impact of missing covariate data.

8.1.1.5 Temporality

Only four studies did not consider or assess exposures prior to NHL diagnosis (Bloemen *et al.*, 2004; Koh *et al.*, 2014; Scherr *et al.*, 1992; Cocco *et al.*, 2010), but about half did not ensure an appropriate period of time between exposure and diagnosis, either in the design or the analysis (*i.e.*, ≥ 0.5 years for NHL [CDC, 2015]). This is likely not a major issue in cohort studies because they were generally large and had